RAMPART (RE06)
PHARMACY MANUAL

An international investigator-led phase III multi-arm multi-stage multi-centre randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

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1 CONTACT DETAILS

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TRIAL INFORMATION	
ISRCTN #	ISRCTN53348826
NCT #	NCT03288532
EudraCT #	2017-002329-39
CTA #	20363/0380/001-0001
REC #	17/LO/1875
Sponsor	The RAMPART trial is an investigator-led academic trial sponsored by UCL and co-ordinated by the MRC CTU at UCL.
Funders	Kidney Cancer UK (clinical trial grant award) AstraZeneca LP (educational grant and free-of-charge durvalumab and tremelimumab)
Chief Investigator	Dr James Larkin

INVESTIGATIONAL MEDICINAL PRODUCT	
IMP 1	Durvalumab (Arm B and C)
IMP 2	Tremelimumab (Arm C)
Marketing Authorisation Holder (MAA)	Astra Zeneca
Distributor	Thermo Fisher

2 INTRODUCTION

This manual includes all essential information on pharmacy operations for the RAMPART trial. It should be read in conjunction with the RAMPART Protocol and must be solely used for the treatment of RAMPART participants.

2.1 TRIAL SUMMARY

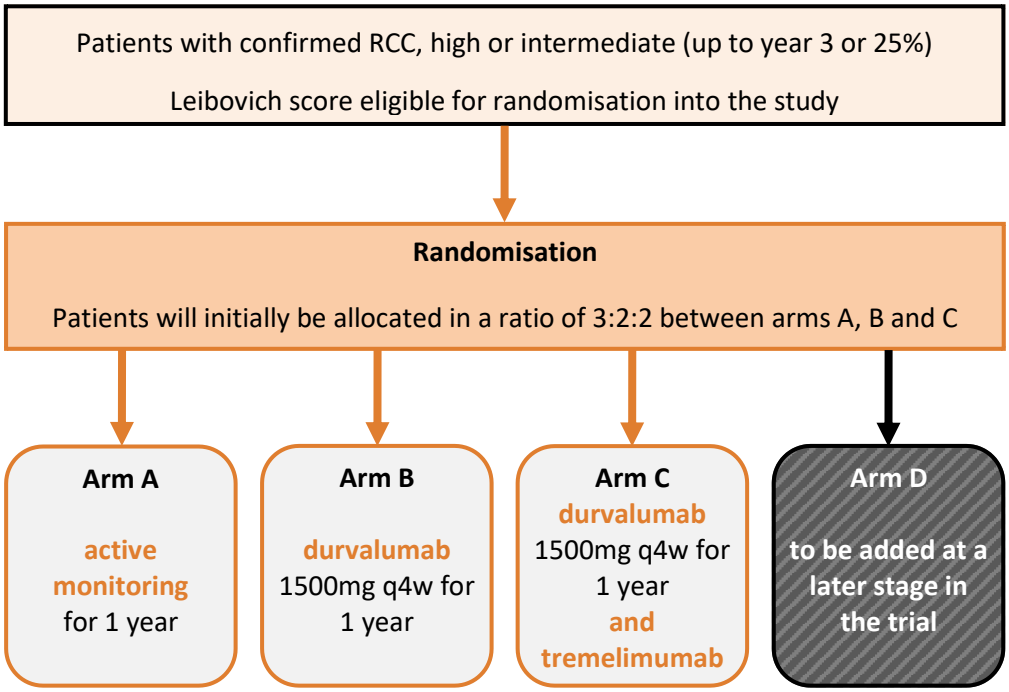
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Study Design	RAMPART is a phase III Multi-Arm, Multi-Stage (MAMS), multi-centre, randomised controlled platform trial.
Type of Participants to be Studied	Patients who have had their RCC resected and are classified as being at intermediate or high risk of recurrence (Leibovich score 3-11) are eligible for randomisation into RAMPART. At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. We will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached.
Setting	The trial will be run at hospitals in the UK, France, Australia, New Zealand and the US.
Interventions to be Compared	Patients will be randomly assigned in a ratio of 3:2:2 (A:B:C) to the following trial arms: • Arm A - active monitoring for 1 year • Arm B - durvalumab (1500mg) 4 weekly for 1 year (13 cycles maximum) • Arm C - durvalumab (administered as per arm B, i.e. 13 cycles maximum) and tremelimumab (75mg) on day 1 and week 4 visits (i.e. 2 cycles).
Study Aims	The RAMPART platform trial has been designed to evaluate multiple treatments simultaneously, while adapting to a changing landscape as data on different agents and combinations of agents emerges. The aims for the initial research comparisons are as follows: • Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase Disease Free Survival (DFS) compared with active monitoring (Arm B vs Arm A, and Arms C vs Arm A respectively)? • Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase Overall Survival (OS) compared with active monitoring in patients classified as Leibovich high-risk (Arm B vs Arm A, and Arms C vs Arm A respectively)?

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Study Hypothesis	Durvalumab is able to prevent tumour relapse by the inhibition of the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway, which plays a critical role in tumour immune evasion. Combination treatment with anti-CTLA4 agent tremelimumab increases immune response and anti-tumour activity.
Co-Primary Outcome Measure(s)	**DFS** and **OS** • DFS is defined as the interval from randomisation to first evidence of local recurrence, new primary RCC, distant metastases, or death from any cause, whichever occurs first. • OS is defined as all-cause mortality, the time from randomisation to death from any cause (including RCC).
Secondary Outcome Measure(s)	• Metastasis Free Survival (MFS), defined as the interval from randomisation to first evidence of metastases or death from RCC. • RCC specific survival time, defined as the time from randomisation to death from RCC. • Quality of life • Toxicity • Patient preferences for adjuvant immunotherapy
Exploratory Objective	To collect blood and tissue samples for defining biological responses to durvalumab and for identifying candidate markers (e.g. PD-L1 expression) that may correlate with likelihood of clinical benefit.
Randomisation	Patients will be randomised centrally using block randomisation across a small number of important stratification factors.
Number of Participants to be Studied	Approximately 1,750 patients will be recruited to the initial three arm design. As RAMPART is an adaptive, platform trial we plan to add at least one additional arm over time. Recruitment across the current three study arms will be: • Arm A - 750 patients • Arm B - 500 patients • Arm C - 500 patients
Duration	The duration of treatment in each of research arms B and C is one year. Follow-up will continue until the primary outcomes have reached maturity. We anticipate reporting on the co-primary outcomes as follows (all times are from the start of recruitment): • DFS in the durvalumab + tremelimumab combination arm (C) after approx. 6.25 years • DFS in the single-agent durvalumab arm (B) after approx. 10.5 years • OS in high-risk patients (Leibovich Score 6-11) in the durvalumab + tremelimumab combination arm (C) after

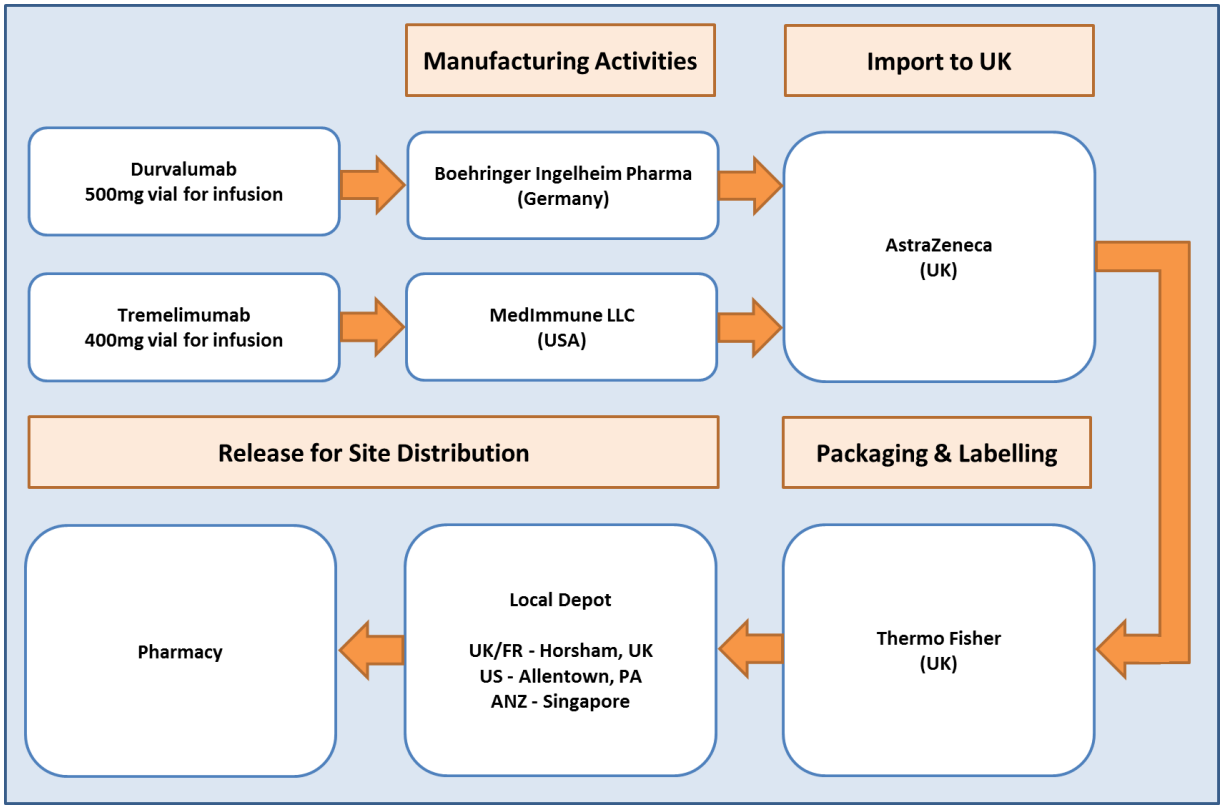
SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	approx. 13.25 years • OS in high-risk patients (Leibovich Score 6-11) in the single-agent durvalumab arm (B) after approx. 20.5 years

Please refer to the RAMPART Protocol for detailed information on eligibility criteria.

Figure 1 Trial Entry, Randomisation and Treatment



2.2 IMP DISTRIBUTION OVERVIEW



3 INVESTIGATION MEDICINAL PRODUCTS

The Investigational Medicinal Products (IMPs) for the RAMPART trial are:

- Durvalumab
- Tremelimumab

Both IMPs are provided free-of-charge by the manufacturer (Astra Zeneca) and distributed by Thermo Fisher.

Durvalumab is a human immunoglobulin (Ig) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand (PD-L1) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells). Tremelimumab is a human immunoglobulin (IgG2) monoclonal antibody (mAb) directed against CTLA-4.

The current Investigator Brochures for both IMPs are included in the **Pharmacy Site File**.

Additional information on the rationale for fixed dosing and combination treatment can be found in the RAMPART Protocol.

The research arms are:

- Arm A - active monitoring for 1 year
- Arm B - durvalumab (1500mg) 4 weekly for 1 year (13 cycles maximum)
- Arm C - durvalumab (administered as per arm B, i.e. 13 cycles maximum) and tremelimumab (75mg) on day 1 and week 4 visits (i.e. 2 cycles).

3.1 TREMELIMUMAB

3.1.1 TREMELIMUMAB FORMULATION

Tremelimumab will be supplied as a 400mg vial solution for infusion. The solution contains 20mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20 mL.

3.1.2 TREMELIMUMAB STORAGE

Investigational medicinal product vials are stored at 2°C to 8°C and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

Supplies of tremelimumab must be kept in a secured temperature-controlled area where access is restricted to designated pharmacy staff. Sites should ensure that supplies for use in the RAMPART trial are segregated from trial supplies that are used in any other study or non-study commercial supplies.

Should the IMP be exposed to temperatures above/below the range specified above, then this must be treated as a temperature excursion. All temperature deviations **must** be reported to the RAMPART team as per **Section 6.**

Temperature logs must be maintained using calibrated temperature monitoring equipment in order to demonstrate that the study drug has been stored at all times under the correct storage conditions. Calibration certificates for temperature monitoring equipment must also be retained and available for review as required. Temperature logs should either be filed in the **Pharmacy Site File** or a file note inserted to indicate the storage location of the logs.

3.1.3 TREMELIMUMAB PREPARATION

The dose of tremelimumab must be prepared using aseptic technique in line with local hospital procedures. Doses of 75 mg tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter.

Procedure: Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8mL of tremelimumab (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1mg/mL to 10mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed.

3.1.4 TREMELIMUMAB STABILITY

Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C
- 4 hours at room temperature

If in-use preparation and/or storage time exceeds the limits, a new dose must be prepared from new vials.

It is recommended that the prepared final IV bag be stored in the dark until needed. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature as per local guidance prior to administration.

3.1.5 TREMELIMUMAB LABELLING

The outer carton and vials for both IMPs will be labelled by the distributor. Master labels are provided in the **Pharmacy Site File**.

Once reconstituted and prepared, the IV bag should be labelled according to local hospital procedures and Annex 13 labelling requirements.

3.1.6 TREMELIMUMAB ADMINISTRATION

Tremelimumab Administration (Arm C)	
Tremelimumab dose	75 mg (fixed)
Route	Intravenous (IV)
Schedule	Q4W on D1 and D1 of Week 4 cycles (**maximum 2 cycles**)
Number of maximum cycles	2
Cycle	28 days

Tremelimumab Administration (Arm C)	
Last cycle delivered on	Week 4
Permissible treatment delays	Administrative delay of 3 days either side of expected infusion date. Any delays exceeding 3 days should be discussed with the RAMPART TMT.
Missed cycles	If time between infusions exceeds 8 weeks then the treatment **must** be permanently discontinued. In practice this means a patient may miss a single infusion before having to resume treatment at their next scheduled visit.
Administration	***Please note that for Arm C patients, the tremelimumab infusion must be administered before durvalumab.*** 1. At room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein 2. The entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22µm in-line filter; less than 55 minutes is considered a deviation. 3. If there are interruptions during the tremelimumab infusion, the maximum time for IV bag infusion should not exceed 8 hours at room temperature. In the event that the infusion time exceeds the 8 hour time limit, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded. 4. The IV line will be flushed with a volume of 0.9% (w/v) saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. 5. **On the first dosing occasion**, **the durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion**. A 1-hour **observation period** is also required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent post-infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).
Hold and Infusion times	From needle puncture to start of administration: • 4 hours at room temperature • 24 hours at 2°C to 8°C IV bag infusion, including interruptions: 8 hours at room temperature
Dose modifications	If a patient's **weight falls to 30kg or below** the patient should receive weight-based dosing equivalent to **1mg/kg tremelimumab Q4W until the weight improves to >30 kg**, at which point the patient should start receiving the fixed dosing of tremelimumab of

Tremelimumab Administration (Arm C)	
	75 mg Q4W.

3.2 DURVALUMAB

3.2.1 DURVALUMAB FORMULATION

Durvalumab is supplied as a 500mg vial solution for infusion. The solution contains 50mg/ML durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10mL.

3.2.2 DURVALUMAB STORAGE

IMP vials are stored at 2°C to 8°C and must not be frozen. The vials should be protected from light by storing in an opaque container. Durvalumab must be used within the individually assigned expiry date on the label.

Supplies of durvalumab must be kept in a secured temperature-controlled area where access is restricted to designated pharmacy staff. Sites should ensure that supplies for use in the RAMPART trial are segregated from trial supplies that are used in any other study or non-study commercial supplies.

Should the IMP be exposed to temperatures above/below the range specified above, then this must be treated as a temperature excursion. All temperature deviations **must** be reported to the RAMPART team as per **Section 6.**

Temperature logs must be maintained using calibrated temperature monitoring equipment in order to demonstrate that the study drug has been stored at all times under the correct storage conditions. Calibration certificates for temperature monitoring equipment must also be retained and available for review as required. Temperature logs should either be filed in the **Pharmacy Site File** or a file note inserted to indicate the storage location of the logs.

3.2.3 DURVALUMAB PREPARATION

The dose of durvalumab must be prepared using aseptic technique in line with local hospital procedures. A fixed dose of 1500mg durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20mg/mL, and delivered through an IV administration set with a 0.2 or 0.22µm in-line filter.

Procedure: Remove 30.0mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0mL of durvalumab (i.e., 1500mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20mg/mL (IV bag volumes 100 to 1000mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

3.2.4 DURVALUMAB STABILITY

Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C

- 4 hours at room temperature

If in-use preparation and/or storage time exceeds the limits, a new dose must be prepared from new vials.

Infusion solutions must be allowed to equilibrate to room temperature as per local guidance prior to commencement of administration.

3.2.5 DURVALUMAB LABELLING

The outer carton and vials will be labelled by the distributor. Master labels are provided in the **Pharmacy Site File**.

Once reconstituted and prepared, the IV bag should be labelled according to local hospital procedures and Annex 13 labelling requirements.

3.2.6 DURVALUMAB ADMINISTRATION

Durvalumab Administration (Arms B and C)	
Durvalumab dose	1500mg (fixed)
Route	Intravenous (IV)
Schedule	Q4W for 1 year maximum (**must not exceed 1 year**)
Number of maximum cycles	13
Cycle	28 days
Last cycle delivered on	Week 48
Permissible treatment delays	Administrative delay of 3 days either side of expected infusion date. Any delays exceeding 3 days **must** be discussed with the RAMPART TMT.
Missed cycles	If time between infusions exceeds 8 weeks then the treatment **must** be permanently discontinued. In practice this means a patient may miss a single infusion before having to resume treatment at their next scheduled visit.
Administration	***Please note that for Arm C patients, the tremelimumab infusion must be administered before durvalumab.*** 1. At room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein 2. The entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22µm in-line filter; less than 55 minutes is considered a deviation. 3. If there are interruptions during the durvalumab infusion, the maximum time for IV bag infusion should not exceed 8 hours at room temperature. In the event that the infusion time exceeds the 8 hour time limit, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded. 4. The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set

Durvalumab Administration (Arms B and C)	
	used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.
Hold and Infusion times	From needle puncture to start of administration: • 4 hours at room temperature • 24 hours at 2°C to 8°C IV bag infusion, including interruptions: 8 hours at room temperature
Dose modifications	If a patient's **weight falls to 30kg or below** the patient should receive weight-based dosing equivalent to **20 mg/kg of durvalumab Q4W until their weight improves to >30 kg,** at which point the patient should start receiving the fixed dosing of durvalumab 1500mg Q4W.

3.2.7 TREATMENT DISCONTINUATION

An individual patient may stop treatment early or have treatment stopped early for any of the following reasons:

- Disease progression
- Unacceptable toxicity Intercurrent illness that prevents further treatment
- Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational medicinal product might constitute a safety risk.
- Pregnancy or intent to become pregnant
- Grade ≥3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Withdrawal of consent for treatment by the patient

3.2.8 SAFETY ASSESSMENTS

All patients will undergo a number of screening tests to assess eligibility; furthermore a pregnancy test will be carried out on all pre-menopausal female patients prior to randomisation (serum HCG).

Patients randomised to Arm B and C will also require repeated safety assessments **within a maximum of 3 days** prior to each treatment administration and up to 120 days after last protocol treatment. This will be at Month 15 if treatment is completed as per protocol or sooner if treatment is discontinued early. A pregnancy test will also be required on all pre-menopausal female participants prior to each treatment administration (urine HCG or serum HCG if there is any doubt over the results of the urine test).

Failure to perform any of the safety tests will be considered a protocol violation and will need to be reported as described in **Section 6.**

A full list of the safety lab tests (screening and pre-treatment) is provided in the **RAMPART Trial Protocol** and Pharmacy training slides (both available in the **Pharmacy Site File** and **RAMPART website**).

Toxicity Management Guidelines are also provided in the **RAMPART Protocol Appendices**.

3.2.9 CONMEDICATIONS

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "not permitted" in **Table 2** .

Table 1 Permitted Medications

RESCUE, SUPPORTIVE MEDICATION OR CLASS OF DRUG	USAGE
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" below.	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, other treatments as necessary])	Should be used when necessary for all patients
Opioids	Can be used with caution and under medical control after discussion with the Trial Physician
Inactivated viruses	Can be used when necessary for all patients

Table 2 Prohibitive Medications

PROHIBITED MEDICATION OR CLASS OF DRUG	USAGE
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment

PROHIBITED MEDICATION OR CLASS OF DRUG	USAGE
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers.	Should not be given during the study. (Use of immunosuppressive medications for the management of durvalumab or tremelimumab related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses [e.g., food allergies or CT scan contrast hypersensitivity] are acceptable upon discussion with the Trial Physician
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
Live attenuated vaccines	Should not be given through 30 days after the last dose of durvalumab or tremelimumab.

4 DRUG ORDERING AND RE-SUPPLY

4.1 INITIAL SHIPMENT AND STARTER PACK

Once activation greenlight has been given by the RAMPART TMT, an initial shipment will be triggered to ensure sufficient stock is available to treat prospective patients.

The initial starter pack will include:

- 5 durvalumab cartons (15 vials), sufficient to treat 5 patients/5 infusions
- 2 tremelimumab cartons (4 vials), sufficient to treat 4 patients/4 infusions

All shipments must be marked as 'Received' in order to allow the stock to be allocated to a randomised study participant. For more information on how to record receipt of new shipments, please refer to the **Drug Supply Management System (DSMS) User Guide.**

4.2 RE-ORDERING

The re-ordering of trial stock will be managed automatically by DSMS. New shipment requests will be generated and sent to Thermo Fisher whenever stock falls below the re-order thresholds (12 vials of durvalumab or 4 vials of tremelimumab). The size of the shipment will be based on the number of patients currently on treatment at your site. The Pharmacy and Research teams will receive an email notification once a new shipment has been dispatched.

If you have any concerns about the amount of stock at site (low or high), please contact the RAMPART TMT who will look into the matter.

4.3 ACCESS TO DRUG SUPPLY MANAGEMENT SYSTEM (DSMS)

At site activation, the RAMPART TMT will create DSMS accounts for all members of the pharmacy team who are present on the Delegation Log and have completed the DSMS training, and all other relevant trial specific training (see Section 7 for more details).

Access to DSMS for any new staff will need to be requested through the RAMPART TMT. An updated copy of the Personnel List, Delegation Log and Training Log should be sent with the request.

Once an account is created, the user will received an automated email containing their username, temporary password and a link to DSMS. The password can be changed once you log in to the system for the first time.

For further information about accessing the system, please refer to the **Drug Shipment Management System User Guide**. The RAMPART TMT should be contacted about any problems accessing the system.

5 PRESCRIBING, DISPENSING AND ACCOUNTABILITY

5.1 PRESCRIBING

Participating centres are responsible for devising their own prescription forms; no approval is required by the RAMPART TMT prior to their use. Either paper or electronic prescriptions can be used; if an electronic system is being used the Pharmacy team is responsible for a validation system and ensuring the correct IMP is being prescribed. Paper based prescription must be version controlled and the current template kept in the **Pharmacy Site File**.

However, prescription forms **must** include the following information:

- EudraCT number
- 'Clinical Trial use only'
- Patient ID as given at randomisation
- Trial arm
- Protocol dose. If patients weigh 30kg or less, the weight-adjusted dose

5.2 DRUG ALLOCATION

Once a prescription has been completed, either the Research Nurse or Pharmacist must allocate drug by logging into DSMS and completing a drug allocation form. They will be asked to enter the following details:

- Participant details (trial number, date of birth)
- The visit the participant is attending (so that the system knows what treatment to allocate)

DSMS will tell the user how many packs (vials) should be dispensed. The pack numbers you are given correspond to the batch numbers on the tremelimumab and durvalumab vials. You can pick any vials from the indicated batches.

A summary form containing the pack numbers of the packs to be retrieved, called a Drug Allocation Report, will be generated by DSMS as confirmation. The Pharmacist will receive an automatic email notification letting them know that the dispensing process has been initiated and confirming the pack details.

If the drug allocation is carried out by a Research Nurse, they should pass the Drug Allocation Report and prescription to the pharmacy staff, who can then dispense the required pack(s). If a Pharmacist is carrying out the allocation, they should only do so once they have a copy of the prescription.

If for some reason the allocated packs are not available in pharmacy (for example, if they are found to be damaged or expired, or are missing) DSMS can be used to obtain replacement packs.

Please refer to the **Drug Shipment Management System User Guide** for full details of the drug allocation process.

5.3 DISPENSING

Once reconstituted using aseptic technique, IV bags should be dispensed and handled as per local practice. Participating centres are responsible for ensuring products are labelled as IMP using local label templates.

Only delegated pharmacy staff must be involved in dispensing activities. Please refer to Section 7 for more information on trial-specific training.

5.4 ACCOUNTABILITY

Drug accountability in RAMPART is being managed via DSMS. Therefore, use of Accountability Logs is not mandated in this trial. However, you can use Accountability Logs if required to adhere to local procedures. A template Accountability Log is available through the RAMPART website or local templates can be used instead.

5.5 RETURNS AND DESTRUCTION

All empty, part used vials and packaging should be destroyed immediatedly after reconciliation of accountability.

Sites are expected to destroy any empty, part-used or expired IMP vials as per local practice. Destruction should be documented on the trial-specific Accountability Log. IMP that has already been reconstituted for IV administration but that it is unused for treatment should also be destroyed as per local practice.

5.6 RECALL

The RAMPART TMT will notify all participating centres of any IMP recalls. The notification should be expected via email and may be followed up by a telephone call. Pharmacy staff should check the IMP receipt documentation to ascertain whether the affect batch of IMP has been received.

Details on the specific recall procedure will be described in the initial notification email along with detailed actions on what to do if the affected IMP was received and/or administered. All affected stock **must be quarantined** until further notice by the RAMPART TMT.

6 TEMPERATURE DEVIATIONS AND PROTOCOL VIOLATIONS

All temperature deviations should be notified to the RAMPART TMT via email. Stock must be destroyed as described in **Section 5.5.** For more information on storage conditions, please see **Section 3.1.2** and **Section 3.2.2.**

All protocol violations should be notified to the RAMPART TMT via email. A Corrective and Preventative Action Plan should also be drafted and emailed to the RAMPART TMT for review.

7 TRAINING

All key pharmacy staff will undergo trial-specific training at the time of initial activation. Training will take place via teleconference and training slides will be made available via the **RAMPART website** and the **Pharmacy Site File**.

Refresher training will be arranged throughout the course of the trial; centres are encouraged to ensure all delegated pharmacy staff has attended a recent training session.

The Training Log should be updated upon completion of training at activation and a copy provided as part of the activation process (see **Section** Error! Reference source not found. for more information). Any new member of the pharmacy staff must undergo training before being involved in any trial procedures. Ad hoc training can be arranged via the RAMPART TMT or with an existing member of the site team. If arranged by a member of the site team, training must include:

- Review of current Pharmacy slides (available on the RAMPART website)
- Review of the Pharmacy Manual (this document)
- Review of the current RAMPART Protocol and associated training sides

The Training Log must be kept up to date and filed in the **Pharmacy Site File**. The Training Log will be checked at on-site monitoring visit or remotely if requested by the RAMPART TMT.